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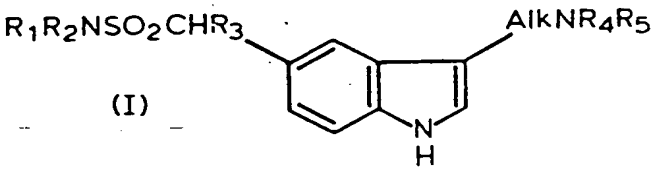
(54) Indoles

(57) Indole derivatives of the general formula



(I)

(where R_1 is H or an alkyl or alkenyl group; R_2 is H, or an alkyl, alkenyl, aryl, aralkyl or cycloalkyl group; R_3 is H or an alkyl group; R_4 and R_5 are independently H or an alkyl or propenyl group or together form an aralkylidene group; and Alk is an optionally substituted alkylene chain) and their physiologically acceptable salts and solvates are potentially useful for the treatment of migraine.

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glycollate); or wetting agents (e.g. sodium lauryl sulphate). The tablets may be coated by methods well known in the art. Liquid preparations for oral administration may take the form of, for example, solutions, syrups or suspensions, or they may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may be prepared by conventional means with pharmaceutically acceptable additives such as suspending agents (e.g. sorbitol syrup, methyl cellulose or hydrogenated edible fats); emulsifying agents (e.g. lecithin or acacia); non-aqueous vehicles (e.g. almond oil, oily esters or ethyl alcohol); and preservatives (e.g. methyl or propyl *p*-hydroxybenzoates or sorbic acid).

For buccal administration the composition may take the form of tablets or lozenges formulated in conventional manner.

The compounds of the invention may be formulated for parenteral administration by injection, including using conventional catheterisation techniques or infusion. Formulations for injection may be presented in unit dosage form e.g. in ampoules or in multi-dose containers, with an added preservative. The compositions may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilising and/or dispersing agents. Alternatively, the active ingredient may be in powder form for reconstitution with a suitable vehicle, e.g. sterile pyrogen-free water, before use.

The compounds of the invention may also be formulated in rectal compositions such as suppositories or retention enemas, e.g. containing conventional suppository bases such as cocoa butter or other glycerides.

For administration by inhalation the compounds according to the invention are conveniently delivered in the form of an aerosol spray presentation from pressurised packs or a nebuliser, with the use of a suitable propellant, e.g. dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas. In the case of a pressurised aerosol the dosage unit may be determined by providing a valve to deliver a metered amount. Capsules and cartridges of e.g. gelatin for use in an inhaler or insufflator may be formulated containing a powder mix of a compound of the invention and a suitable powder base such as lactose or starch.

A proposed dose of the compounds of the invention for oral, parenteral, rectal or buccal administration to man for the treatment of migraine is 0.1 to 100 mg of the active ingredient per dose which could be administered, for example 1 to 4 times per day.

Aerosol formulations are preferably arranged so that each metered dose or "puff" of aerosol contains 20 μg–1000 μg of a compound of the invention. The overall daily dose with an aerosol will be within the range 100 μg–10 mg. Administration may be several times daily, for example 2, 3, 4 or 8 times, giving for example 1, 2 or 3 doses each time. The overall daily dose and the metered dose delivered by capsules and cartridges in an inhaler or insufflator could be double those with aerosol formulations.

A preferred class of compounds represented by the general formula (I) is that in which R_1 represents a hydrogen atom or a C_{1-6} alkyl group and R_2 represents a hydrogen atom or a C_{1-3} alkyl, C_{3-6} alkenyl or ar(C_{1-4})alkyl group.

Another preferred class of compounds represented by the general formula (I) is that in which R_3, represents a hydrogen atom.

A further preferred class of compounds is that wherein, in the general formula (I), R_4 and R_5, which may be the same or different, each represents a hydrogen atom or a C_{1-3} alkyl group, for example, a methyl group.

A preferred class of compounds falling within the scope of general formula (I) is that wherein R_1 represents a hydrogen atom or a C_{1-3} alkyl group e.g. a methyl group; R_2 represents a hydrogen atom or a C_{1-3} alkyl group, e.g. a methyl, ethyl or isopropyl group, a C_{3-4} alkenyl group e.g. a propenyl group or an ar(C_{1-2})alkyl group e.g. a benzyl group; R_3 represents a hydrogen atom; and R_4 and R_5, which may be the same or different, each represents a hydrogen atom or a C_{1-3}alkyl group e.g. a methyl group; and physiologically acceptable salts and solvates (e.g. hydrates) thereof.

A particularly preferred class of compounds according to the invention is that wherein R_1 represents a hydrogen atom or a C_{1-3} alkyl group e.g. a methyl group; R_2 represents a C_{1-3} alkyl group e.g. a methyl group, or a C_{3-4} alkenyl group e.g. a propenyl group; R_3 and R_4 each represents a hydrogen atom; and R_5 represents a hydrogen atom or a C_{1-3} alkyl group e.g. a methyl group; and physiologically acceptable salts and solvates (e.g. hydrates) thereof.

Preferred compounds according to the invention include:-

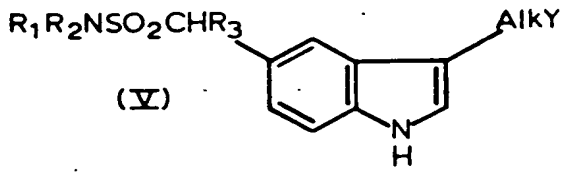
3-(2-(methylamino)ethyl)-N-methyl-1*H*-indole-5-methanesulphonamide;

3-(2-aminoethyl)-N,N-dimethyl-1*H*-indole-5-methanesulphonamide;

3-(2-aminoethyl)-N-(2-propenyl)-1*H*-indole-5-methanesulphonamide;

and physiologically acceptable salts and solvates (e.g. hydrates) of these compounds. A particularly preferred compound according to the invention is:-

3-(2-aminoethyl)-N-methyl-1*H*-indole-5-methanesulphonamide and the physiologically acceptable salts (e.g. the hydrochloride and succinate salts) and solvates (e.g. hydrates) thereof.



(V)

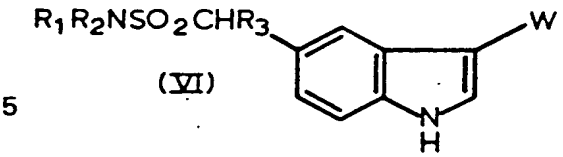
(wherein Y is a readily displaceable group)
or a protected derivative thereof, with a compound of formula R_4R_5NH.

This displacement reaction may conveniently be carried out on those compounds of formula (V) wherein the substituent group Y is a halogen atom (e.g. chlorine, bromine or iodine) or a group OR where OR is, for example, an acyloxy group, such as acetoxy, chloroacetoxy, dichloroacetoxy trifluoroacetoxy, or *p*-nitrobenzoloxy or a sulphonate group (e.g. *p*-toluene sulphonate or methyl sulphonate).

The above reaction is conveniently effected in an inert organic solvent (optionally in the presence of water), examples of which include alcohols, e.g. ethanol; ethers, e.g. tetrahydrofuran; esters e.g. ethyl acetate; amides e.g. N,N-dimethylformamide; and ketones e.g. acetone. The process may be carried out at a temperature of, for example, -10 to $+150$°C, preferably 20 to 50°C.

The compounds of formula (V) wherein Y is a halogen atom may be prepared by reacting a hydrazine of formula (III) with an aldehyde (or a protected derivative thereof) of formula (IV) in which Q is a halogen atom, in an aqueous alcohol (e.g. methanol) or an aqueous ether (e.g. dioxan) containing an acid (e.g. acetic or hydrochloric acid) or by reacting a compound of general formula (V) wherein Y is a hydroxy group with the appropriate phosphorus trihalide. The intermediate alcohol, wherein Y is a hydroxy group, may also be used to prepare compounds of formula (V), wherein Y is a group OR, by acylation or sulphonylation with the appropriate activated species (e.g. anhydride or sulphonyl chloride) using conventional techniques.

Compounds of general formula (I) may also be prepared by another general process (C) involving reduction of a compound of general formula (VI):



(VI)

(wherein W is a group capable of being reduced to give the required $AlkNR_4R_5$ group or a protected derivative thereof)
or a salt or protected derivative thereof.

The required Alk and NR_4R_5 groups may be formed by reduction steps which take place separately or together in any appropriate manner.

Examples of groups represented by the substituent group W include the following:-

TNO_2 (where T is Alk or an alkenyl group corresponding to the group (Alk); $AlkN_3$; $AlkNR_4COR_5'$; $-COCONR_4R_5$; $(CHR_6)_xCHR_7CN$; CHR_7COZ; $(CHR_6)_xCR_7 = NOH$; $CH(OH)CHR_7NR_4R_5$; $COCHR_7Z$ (wherein R_6 and R_7 which may be the same or different, each represents a hydrogen atom or a C_{1-3} alkyl group, Z is an azido group N_3 or the group NR_4R_5 or a protected derivative thereof, x is zero or 1 and R_5' is part of the group R_5 or the group OR_c where R_c is an alkyl or an aralkyl group).

Groups which may be reduced to the group Alk include corresponding unsaturated groups and corresponding groups containing one or more hydroxyl groups or carbonyl functions.

Groups which may be reduced to the group NR_4R_5 wherein R_4 and R_5 are both hydrogen include nitro, azido, hydroxyimino and nitrile groups. Reduction of a nitrile group yields the group CH_2NH_2 and thus provides a methylene group of the group Alk.

The required NR_4R_5 group wherein R_4 and/or R_5 are other than hydrogen may be prepared by reduction of a nitrile $(CHR_6)_xCHR_7CN$ or an aldehyde $(CHR_6)_xCHR_7CHO$ (wherein R_6, R_7 and x are as previously defined) in the presence of an amine, R_4R_5NH.

A particularly suitable method for preparing a compound of formula (I) wherein R_4 and/or R_5 is other than hydrogen, is reductive alkylation of the corresponding compound wherein R_4 and/or R_5 represents hydrogen, with an appropriate aldehyde or a ketone (e.g. acetaldehyde or benzaldehyde or acetone) in the presence of a suitable reducing agent. In some instances (e.g. for the introduction of the group R_5 where R_5 is ethyl) the aldehyde (e.g. acetaldehyde) may be condensed with the primary amine and the intermediate thus formed may subsequently be reduced using a suitable reducing agent.

it may be necessary to protect the group NR_4R_5, wherein R_4 and/or R_5 represents hydrogen, with a group easily removable at the end of the reaction sequence. Such groups may include, for example, aralkyl groups, such as benzyl, diphenylmethyl or triphenylmethyl; or acyl groups such as N-benzyloxycarbonyl or t-butoxycarbonyl or phthaloyl.

In some cases, it may also be desirable to protect the indole nitrogen with, for example, an aralkyl group such as benzyl.

Subsequent cleavage of the protecting group may be achieved by conventional procedures. Thus an aralkyl group such as benzyl, may be cleaved by hydrogenolysis in the presence of a catalyst (e.g. palladium on charcoal) or sodium and liquid ammonia; an acyl group such as N-benzyloxycarbonyl may be removed by hydrolysis with, for example, hydrogen bromide in acetic acid or by reduction, for example by catalytic hydrogenation. The phthaloyl group may be removed by hydrazinolysis (e.g. by treatment with hydrazine hydrate) or by treatment with a primary amine (e.g. methylamine).

Where it is desired to isolate a compound of the invention as a physiologically acceptable salt, for example as an acid addition salt, this may be achieved by treating the free base of general formula (I), with an appropriate acid (e.g. succinic or hydrochloric acid) preferably with an equivalent amount in a suitable solvent (e.g. aqueous ethanol).

The starting materials or intermediate compounds for the preparation of the compounds according to this invention may be prepared by conventional methods analogous to those described in U.K. Published Patent Application No. 2035310.

As well as being employed as the last main step in the preparative sequence, the general methods indicated above for the preparation of the compounds of the invention may also be used for the introduction of the desired groups at an intermediate stage in the preparation of the required compound. Thus, for example, the required group at the 5-position may be introduced either before or after cyclisation to form the indole nucleus. It should therefore be appreciated that in such multi-stage processes, the sequence of reactions should be chosen in order that the reaction conditions do not affect groups present in the molecule which are desired in the final product.

The invention is further illustrated by the following Examples. All temperatures are in °C.
The invention is further illustrated by the following examples. All temperatures are in °C. 'Hyflo' is a filtration aid. Chromatography was carried out using silica gel (Merck, Kieselgel 60, Art. 7734) and t.l.c.-thin layer chromatography, on silica (Macherly-Nagel, Polygram) except where otherwise stated. The following abbreviations define the eluent used for chromatography and t.l.c.

(A) Methylene chloride–ethanol–0.88 ammonia 100:8:1
(B) Methylene chloride–ethanol–0.88 ammonia 40:8:1
(C) Cyclohexane–ethyl acetate 1:4
(D) Ethyl acetate–toluene 1:1
(E) Ethyl acetate–toluene 3:7
(F) Methylene chloride–ethanol–0.88 ammonia 30:8:1
(G) Methylene chloride–ethanol–0.88 ammonia 150:8:1
(H) Methylene chloride–ethanol–0.88 ammonia 25:8:1
(I) Chloroform–methanol 97:3
(J) Methylene chloride–ethanol–0.88 ammonia 20:8:1
(K) Ethyl acetate–isopropanol–water–0.88 ammonia 20:10:8:1
(L) Ethyl acetate–isopropanol–water–0.88 ammonia 25:15:8:2
(M) Methylene chloride–methanol 95:5
(N) Methylene chloride–ethanol–0.88 ammonia 50:8:1
(O) Methylene chloride–ethanol–0.88 ammonia 10:8:1
(P) Chloroform–methanol 95:5
(Q) Methylene chloride–ethanol–0.88 ammonia 200:8:1

Intermediates were routinely checked for purity by t.l.c. employing u.v. light for detection and spray reagents such as DNP and potassium permanganate. In addition indolic intermediates were detected by spraying with aqueous ceric sulphate and tryptamines by spraying with a colution of iodoplatinic acid or ceric sulphate.

Example 1

3-(2-Aminoethyl)-N-methyl-1H-indole-5-methanesulphonamide, maleate

(a) *4-Amino-N-methylbenzenemethanesulphonamide, hydrochloride*

A suspension of N-methyl-4-nitrobenzenemethanesulphonamide (30g) in ethanol (150ml), water (300ml) and hydrochloric acid (2N, 65ml) was hydrogenated over 10% palladium oxide on charcoal (7.5g, 50% paste with water) until hydrogen uptake ceased (9.75l). The catalyst was

Example 3
3-(2-Aminoethyl-N-methyl-1H-indole-5-methanesulphonamide
(a) *4-[2-(3-Cyanopropylidene)hydrazino]-N-methylbenzenemethanesulphonamide*
A solution of the product of example 1(b) (2g) and 3-cyanopropanal dimethylacetal (1.4g) in water (25ml) was treated with dilute hydrochloric acid (2N; 5 drops) and stirred for 24h at room temperature. The resulting white solid was filtered off, washed with water (20ml), ether (100ml) and dried in vacuo at 40° to give the *title compound* (2.1g) m.p. 124-125°.

(b) *3-(Cyanomethyl)-N-methyl-1H-indole-5-methanesulphonamide*
A suspension of the product from stage (a)(0.7g) in polyphosphate ester (7g) and chlorform (14ml) was heated at reflux for 5 min. and then poured onto ice. The resulting suspension was stirred with ice for 20 min., then extracted with chloroform (4 × 20ml) and the extract dried. Solvent was then removed and the residue purified by column chromatography (G). The title compound was obtained as a reddish semi-solid (0.38g) which was impure and was employed directly in the next stage.
T.l.c. (G) Rf 0.4 with impurities at Rf 0.44 and 0.46.

(c) *3-(2-Aminoethyl)-N-Methyl-1H-indole-5-methanesulphonamide*
A solution of the product of stage (b) (0.15g) in methanolic ammonia was hydrogenated over pre-reduced rhodium on alumina (5%, 0.15g) for 18h at room temperature and atmospheric pressure. T.l.c (F) showed the solution contained a major component Rf 0.26 identical with that of 3-(2-aminoethyl)-N-methyl-1*H*-indole-5-methanesulphonamide prepared by the method of example 1.

Example 4
3-(2-Aminoethyl)-N-methyl-1H-indole-5-methanesulphonamide
To a solution of the product of example 3(b) (0.15g) in dry tetrahydrofuran (20ml) was added lithium aluminium hydride (0.15g) and the resulting suspension was heated at reflux (under a nitrogen atmosphere) for 1h. Excess lithium aluminium hydride was destroyed by addition of ethyl acetate (5ml), followed by addition of aqueous potassium carbonate (10ml; saturated). The aqueous layer was extracted with ethanol (10ml). Solvent was evaporated under reduced pressure, and the residual oil purified by column chromatography (H) to give the *title compound* slightly impure as an oil (21mg) which was shown by n.m.r. and t.l.c. (F) Rf 0.26 to be identical with a sample prepared by the method of example 1.

Example 5
3.(2-Aminoethyl)-N-methyl-1H-indole-5-methanesulphonamide.
(a) *N-Methyl-4-[2-(4-Nitrobutylidene)hydrazino]lbenzenemethane sulphonamide.*
To a solution of the product of example 1(b) (1g) in water (20ml) was added 4-nitrobutanal (0.5g) and an oil separated within a few minutes. The resulting suspension was extracted with dichloromethane (4 × 20ml), the extracts dried ($MgSO_4$) and the solvent evaporated *in vacuo* to give the *title compound* as a thick oil (1.08g)
Analysis Found: C,45.3;H,5.6;N,17.3.
$C_{12}H_{18}N_4O_4S.0.2H_2O$ requires C,45.6;H,5.2;N,17.7%
T.l.c. isopropyl acetate/cyclohexane (3:1) Rf 0.26

(b) *N-Methyl-3-(2-nitroethyl)-1H-indole-5-methanesulphonamide*
A solution of the product of stage (a) (2g) in chloroform (40ml) and polyphosphate ester (20g) was heated under reflux for 3 min. and then poured onto ice (50g) and sodium bicarbonate (8%, 20ml). The mixture was stirred at room temperature for 30 minutes and extracted with chloroform (4 × 50ml). The organic extracts were dried ($MgSO_4$) and concentrated. The residue was purified by flash chromatography (Merck 9385) (I) to give the *title compound* as an oil (0.72g) which was used in the next stage without further purification.
T.l.c. (Q) Rf 0.26 N.m.r. 5.2, (triplet CH_2 NO_2)

(c) *3-(2-Aminoethyl)-N-methyl-1H-indole-5-methanesulphonamide*
A solution of the product of stage (b) (0.13g) in ethyl acetate (5ml) was hydrogenated over pre-reduced 10% palladium oxide on charcoal (0.2g, 50% paste with water) for 2h, whereupon hydrogen uptake (20ml) ceased. The catalyst was removed by filtration (hyflo) and the filtrate concentrated. The residue was purified by flash chromatography (Kiselgel 9385) to give the *title compound* (8mg) as an oil which was shown by t.l.c. (F) Rf 0.26 to be identical with the product of example 1.

Example 6
3-(2-Aminoethyl)-N-methyl-1H-indole-5-methanesulphonamide

(c) *4-Hydrazino-N-(phenylmethyl)benzenemethanesulphonamide, hydrochloride*
A thick suspension of the product of stage (b) (3.68g) in conc. hydrochloric acid (50ml) was stirred at −5° whilst a solution of sodium nitrate (0.9g) in water (10ml) was added dropwise so that temperature did not exceed 0°. Stirring was continued for 30min. The resulting suspension was filtered to remove starting material and the filtrate added in a few portions to a solution of stannous chloride dihydrate (13.5g) in hydrochloric acid (15ml) at −20° and warmed to ambient temperature. The solid that separated was filtered off and recrystallised from hot methanol (100ml) to give the *title compound* as white plates (0.39g) m.p. 192–193°. The mother liquors afforded a second crop (0.52g).

(d) *3-(2-Aminoethyl)-N-(phenylmethyl)-1H-indole-5-methanesulphonamide, compound with creatinine, sulphuric acid and water (1:1:1:1.2)*
A solution of the product of stage (c) (0.47) and 4-chlorobutanal dimethylacetal (0.24g) in ethanol (50ml) and water (10ml) was heated at reflux for 4h. Solvent was evaporated and the residual oil purified by column chromatography (F) which afforded the tryptamine slightly impure as an oil (0.34g). A second chromatography (K) gave pure free base as an oil (0.1g) which was taken up in hot ethanol (8ml) and water (1ml) and treated with a solution of creatinine and sulphuric acid (1:1,2N,0.15ml). The salt which crystallised on cooling was filtered off, dried in vacuo at 60° and the *title compound* obtained as an off-white powder (0.125g), m.p. 230-231°.

Analysis Found: C,45.9; H,5.7; N,14.6;
$C_{18}H_{21}N_3O_2S.C_4H_7N_3O.H_2SO_4.1.2H_2O$ requires: C,45.7; H,5.3; N,14.2%
T.l.c. (K) Rf 0.41

Example 10
3-(2-Aminoethyl)-N-phenyl-1H-indole-5-methanesulphonamide, compound with creatinine, sulphuric acid and water (1:1:1:1)
(a) *4-Amino-N-phenylbenzenemethanesulphonamide*
A solution of 4-Nitro-N-phenylbenzenemethanesulphonamide (11.0g), in ethyl acetate (400ml) was hydrogenated at room temperature and pressure over pre-reduced 10% palladium oxide on charcoal (1.0g, 50% paste with water) for 4h until hydrogen uptake ceased (2.7l). Methanol (400ml) was added, the catalyst filtered off, and the filtrate evaporated *in vacuo* to give the *title compound* as a white solid (8.98g), m.p. 180–182°.

(b) *4-Hydrazino-N-phenylbenzenemethanesulphonamide, hydrochloride*
By a procedure similar to that described in example 9(c), the product of stage (a) (7.4g) was diazotised and then reduced with stannous chloride to give the *title compound* as a fawn solid (2.0g), m.p. 168–170° (from ethanol).

(c) *3-(2-Aminoethyl)-N-phenyl-1H-indole-5-methanesulphonamide, compound with creatinine, sulphuric acid and water (1:1:1:1)*
By a procedure similar to that described in example 9(d), the product of stage (b) (0.5g) was condensed with 4-chlorobutanal dimethyl acetal (0.25g) to give the tryptamine as an oil. The oil was dissolved in a hot mixture of ethanol (40ml) and water (5ml) and an aqueous solution of creatinine and sulphuric acid (1:1, 2M, 0.9ml) added. Filtration of the cooled mixture acid gave the *title compound* as a pale fawn solid (0.3g), m.p. 198–200°.
Analysis Found: C,45.6; H,5.4; N,14.8.
$C_{17}H_{19}N_3O_2S.C_4H_7N_3O.H_2O_4.H_2O$ requires C,45.2; H,5.4; N,15.0%
T.l.c. (L) Rf 0.4

Example 11
3-(2-Aminoethyl)-N-cyclohexyl-1H-indole-5-methanesulphonamide, compound with creatinine, sulphuric acid, and water (1:1:1:1)
(a) *N-Cyclohexyl-4-nitrobenzenemethanesulphonamide*
By a procedure similar to that described in example 9(a) 4-nitro-benzenemethanesulphonyl chloride (0.3g) was treated with cyclohexylamine (0.36ml) to give the *title compound* (0.25g) m.p. 170–171° (from ethanol).

(b) *4-Amino-N-cyclohexylbenzenemethanesulphonamide*
By a procedure similar to that decribed in example 9(b) the product of stage (a) (6.4g) was hydrogenated to give the *title compound* (5.0g), m.p. 141–143° (from isopropanol).

(c) *N-Cyclohexyl-4-hydrazinobenzenemethanesulphonamide, hydrochloride*
By a procedure similar to that described in example 9(c) the product of stage (b) (1.0g) was

By a procedure similar to that described in example 9(b) the product of stage (a) (7.0g) was hydrogenated in ethanol to give the *title compound* as a white solid (6.0g), m.p. 123–125° (from ethanol).

(c) *4-Hydrazino-N-(2-phenylethyl)benzenemethanesulphonamide, hydrochloride.*
By a procedure similar to that described in example 9(c) the product of stage (b) (4g) was diazotised and reduced to give the *title compound* (3.0g), m.p. 160–163° (from ethanol).

(d) *3-(2-Aminoethyl)-N-(2-phenylethyl)-1H-indole-5-methanesulphonamide, hydrochoride, quarter hydrate.*
By a procedure similar to that described in example 9(d) the product of stage (c) (2.0g) was condensed with 4-chlorobutanal dimethyl acetal (1.0g) and flash chromatographed (Kieselgel 9385) to give the tryptamine as a yellow oil. The oil was dissolved in methanol (10ml) acidified with ethanolic hydrogen chloride (*ca* 2ml) and diluted with ether (200ml). The ether was decanted off the resulting gum, and replaced with more dry ether (200ml). Scratching caused the gum to crystallise, and the resulting solid was filtered off, and dried *in vacuo* to give the *title compound* as a cream solid (0.65g), m.p. 115–119°C.

Analysis Found: C,57.25;H,6.2;N,10.3.
$C_{19}H_{23}N_3O_2S.HCl.0.25H_2O$ requires c,57.3;H,6.2;N,10.5%.
T.l.c. (J) Rf 0.4

Example 14

3-(2-Aminoethyl)-N-(2-propenyl)-1H-indole-5-methanesulphonamide, hydrochloride.

(a) *4-Nitro-N-(2-propenyl)benzenemethanesulphonamide.*
4-Nitrophenylmethanesulphonyl chloride (5.0g) was added dropwise in dry dichloromethane (50ml) to a stirred solution of allylamine (3.3ml) in dry dichloromethane (50ml) at room temperature under nitrogen over 15min. Stirring was continued for 45min. The mixture was washed with water (3 × 50ml), dried ($MgSO_4$) and the solvent evaporated to give a very pale yellow solid (5.22g). A sample (0.26g) was recrystallised from ethanol to give the *title compound* as very pale yellow needles (0.182g), m.p. 118–120.5°.

(b) *4-Amino-N-(2-propenyl)benzenemethanesulphonamide, hydrochloride.*
Sodium borohydride (0.37g) in ethanol (120ml) was added dropwise over 30min to a stirred solution of the product of stage (a) (5.0g) and stannous chloride dihydrate (22g) in ethanol (400ml) at 65° under nitrogen. After stirring at 65° for a further 30min, the mixture was cooled in an ice bath, and iced water (400ml) followed by 5N sodium hydroxide (40ml, to pH 8) were added, giving a milky emulsion. The ethanol was evaporated at reduced pressure, more 5N sodium hydroxide (110ml) was added, and the mixture was extracted with ethyl acetate (3 × 250ml). The organic layers were washed with brine, dried ($MgSO_4$) and evaporated to give a yellow solid (4.96g). A sample (0.3g) was dissolved in ethanol (1.5ml), and ethanolic hydrogen chloride (*ca* 3M, 0.6ml) was added giving a pale yellow precipitate which was filtered off and dried in vacuo at 45°, to give the *title compound* as pale yellow crystals (0.239g), m.p. 153.5–155°.

(c) *4-Hydrazino-N-(2-propenyl)benzenemethanesulphonamide, hydrochloride.*
A solution of sodium nitrite (1.06g) in water (2.5ml) was added dropwise to a stirred suspension of the product from stage (b) (3.5g) in 5N hydrochloric acid (28ml) between −8° and −3° under nitrogen and stirring was continued at *ca* −3° for 80min. The mixture was filtered, and the clear yellow filtrate was added dropwise from an ice-cooled, jacketed dropping funnel to a stirred solution of stannous chloride dihydrate (17.5g) in concentrated hydrochloric acid (17.5ml) between −2° and +1° over 35min. After warming up to 10° over 15min, the mixture was filtered, and the residue was washed with concentrated hydrochloric acid (4 × 5ml) and dry ether (4 × 30ml) and dried to give the *title compound* as a very pale yellow solid (2.44g), m.p. 163–166°, containing 5% inorganic material.

(d) *3-(2-Aminoethyl)-N-(2-propenyl)-1H-indole-5-methanesulphonamide, hydrochloride.*
The product from stage (c) (1.5g) was heated under reflux with 4-chlorobutanol dimethyl acetal (0.83g) in 5:1 ethanol:water (75ml) with stirring under nitrogen for 1.5h. The mixture was poured into 8% aqueous sodium bicarbonate (25ml), and the ethanol was evaporated off at room temperature (vacuum pump). The mixture was extracted with ethyl acetate (4 × 40ml) and the organic layers were washed with brine, dried ($MgSO_4$) and evaporated to give a brown oil (1.62g). Further extraction of the aqueous layers with butanone (3 × 40ml), drying ($MgSO_4$) and

to a cold (− 5°) stirred solution of stannous chloride (16.52g) in concentrated hydrochloric acid (30ml) keeping the solution below 0°.
After allowing the mixture to warm up to room temperature over a period of 1h, the suspension was filtered and the solid washed with ether to give the *title compound* as a white aolid (2.06g), m.p. 169–170°.

(c) *3-(2-Aminoethyl)-N-ethyl-1H-indole-5-methanesulphonamide maleate hemihydrate compound with diethylether* (10:10:5:1)
A solution of the product of stage (b) (0.425g) and 4-chlorobutanal dimethyl acetal (0.244g) in ethanol-water (5:1) (20ml) was stirred at 50° for 40min. Ammonium acetate (0.7394g) was added and then the pH of the solution adjusted to pH 4 by hydrochloric acid. The resultant solution was heated under reflux for 2h.
The pale brown mixture was diluted water (200ml) and washed with ethyl acetate (3 × 100ml). The aqueous solution was basified with potassium carbonate (solid) and then extracted with ethyl acetate (4 × 100ml). Subsequent evaporation of the dried ($MgSO_4$) organic extracts yielded a brown foam (0.38g) which was purified by chromatography (N) to give the tryptamine as a pale brown gum (0.1435g).
A solution of the base (0.1435g, in methanol (2ml) was treated with maleic acid (0.05916g) in methanol (2ml). Subsequent evaporation of the clear solution under reduced pressure gave a pale brown gum which was triturated with anhydrous diethyl ether to present the title compound as a cream powder (0.09g), m.p. 139–142°
T.l.c. (H) Rf 0.4

Analysis Found: C,50.1;H,5.8;N,9.4;
$C_{13}H_{19}N_3O_2S.C_4H_4O_4 0.5H_2 0.0.1C_4H_{10}O$ C,50.5:H,6.1;N, *10.2%*

Example 17
3-(2-Aminoethyl)-1H-indole-5-methanesulphonamide, hydrochloride.
(a) *4-Aminobenzenemethanesulphonamide.*
A suspension of 4-nitrobenzenemethanesulphonamide (7.11g) and 5% palladium oxide on charcoal (1.4g) in ethanol (1.1l) was hydrogenated at room temperature and pressure. The reaction was terminated after 2.5l of hydrogen had been absorbed and the catalyst was removed by filtration. The filtrate was concentrated to give the *title compound* as a solid (4.72g). Recrystallisation of a sample from ethanol gave analytically pure material m.p. 166° (bubbles).

(b) *4-Hydrazinobenzenemethanesulphonamide hydrochloride.*
A solution of sodium nitrate (1.12g) in water (10ml) was added dropwise with stirring over a period of 10min to a paste of the product of stage (a) (3.0g) in conc. hydrochloric acid (4.8ml) at 0 to − 5°. The mixture was chilled to − 5° and added in portions over 10min to a vigorously stirred solution of sodium sulphate (5.02g) and sodium acetate (5g) in water (40ml) at 0 to − 5°. After 20min the mixture was allowed to warm to room temperature over 1h and was then heated at 75–85° for 1h. The solution was filtered and acidified with conc. hydrochloric acid (5.2ml) and heated at 80–85° and then more conc. hydrochloric acid (28ml) was added. The solution was then chilled and the *title compound* separated as a cream solid (2.15g), which was used in the next stage without further purification.
T.l.c. methanol-ethyl acetate, (1:4) Rf 0.6, 0.9 (minor).

(c) *3-[2-(1,3-Dihydro-1,3-dioxo-2H-isoindol-2-yl)ethyl]-1H-indole-5-methanesulphonamide.*
A mixture of 2-(4,4-diethoxybutyl)-1*H*-isoindole-1,3(2H)-dione (0.58g), the product of stage (b) (0.51) and 50% aqueous acetic acid (20ml) was warmed to give a yellow solution which was then boiled in an atmosphere of nitrogen for 2h. The mixture was cooled and extracted with ethyl acetate (5 × 25ml). The extracts were washed with water (3 × 30ml), dried (Na_2SO_4) and concentrated to a gum which on trituration with ether gave a cream solid (0.57g). This was chromatographed eluting with ethyl acetate to give the product as a gum which solidified on trituration with ether. This material (0.29g) was absorbed from acetone onto a PLC plate (Merck Kieselgel 60 F254, 20 × 20cm) and eluted twice with ethyl acetate-cyclohexane (1:1). The pure indole was isolated from the stationary phase by Soxhlet extraction with ether for a day.
Removal of the solvent gave a gum which in trituration with ethyl acetate gave the *title compound* as a cream solid, m.p. 186–188° (32mg).

(d) *3-(2-Aminoethyl)-1H-indole-5-methanesulphonamide, hydrochloride.*
The product of stage (c) (0.3g) was taken up in a solution of methylamine in ethanol (38%, 8ml) to give a clear yellow solution which was kept at room temperature for 3h. Solvent was

hot ethanol (10ml) and a solution of maleic acid (0.1g) in ethanol (3ml) was added. Ether (10ml) was added until a cloudy solution resulted. On cooling the *title compound* deposited as a cream powder (75mg), m.p. 153–154°.

Analysis Found: C,50.0;H.5.4;N,10.8.
$C_{12}H_{17}N_3O_2S.C_4H_4O_4$ requires C,50.4;H,5.0;N,11.0%.
T.l.c. (O) Rf 0.27.

Example 20
3-[2-(Ethylamine)ethyl]-1H-indole-5-methanesulphonamide, hydrochloride, hemihydrate, compound with ethanol (5:5:2:5:1)
A solution of the product of example 19(b) (0.32g) in ethanolic ethylamine (30ml; 33%w/w) was hydrogenated over pre-reduced 10% palladium oxide on charcoal (0.4g, 50% aqueous paste) in ethanol (10ml) at room temperature and atmospheric pressure overnight. The catalyst was removed by filtration (Hyflo) and the filtrate concentrated to an oil (0.30g). Chromatography (O) gave the free base as a foam (0.28g). A solution of the tryptamine (0.28g) in absolute ethanol (10ml) and methanol (10ml) was treated with ethanolic hydrogen chloride (ice cooling) to pH 1, ether (20ml) was added and the resulting suspension was left in the fridge overnight. The *title compound* was filtered off as a white powder (0.24g) m.p. 143–144°.

Analysis Found: C,48.1; H,6.3; N,12.4.
$C_{13}H_{19}N_3O_2S.HCl.05H_20.0.2C_2H_6O$ requires C,47.9; H,6.7; N,12.5%.
T.l.c. (O) Rf 0.48.

Example 21
3-[2-(Dimethylamino)ethyl]-1H-indole-5-methanesulphonamide, hydrochloride, compound with isopropanol (10:10:1:5)
A solution of the product of example 19 (b) (0.2g) in methanolic dimethylamine (1:1, 20ml was hydrogenated over pre-reduced 10% palladium oxide on charcoal (0.4g, 50% aqueous paste) in methanol (10ml) at room temperature and atmospheric pressure for 5h. The catalyst was removed by filtration (hyflo) and the filtrate was concentrated to an oil. Chromatography (B) gave the tryptamine as a white foam (0.16g). Ethanolic hydrogen chloride was added dropwise to a cold solution (ice bath) of the free base in isopropanol (4ml) (until pH4) and the *title compound* was precipitated as a white powder (0.14g) m.p. 237–239°.

Analysis Found: C,49.1; H,6.5; N,12.6.
$C_{13}H_{19}N_3 \times {}_2S.HCl.0.15C_3H_8O$ requires C,49.4; H,6.5; N,12.9%.
T.l.c. (B) Rf 0.23

Example 22
N-Methyl-3-[2-(methylamino)ethyl]-1H-indole-5-methanesulphonamide, compound with maleic acid and ethanol (10:10:1)
A solution of the product of example 2(b) (0.9g) in dry tetrahydrofuran (20ml) was added to a suspension of lithium aluminium hydride (0.9g) in dry tetrahydrofuran (100ml) and heated for 2h at reflux. The resulting suspension was cooled, treated with saturated solution of potassium carbonate (ice cooling), extracted with methanol (3 × 25ml) and the extract concentrated. The residual oil was purified by column chromatography (K) to give the tryptamine as an oil (0.37g). This was dissolved in absolute ethanol (5ml) and treated with ethanolic maleic acid (0.5M; 2.6ml). A sticky precipitate separated. Methanol was added dropwise until a clear solution resulted which was then concentrated under reduced pressure to approx. 1ml and the *title compound* crystallised as an off-white solid (0.2g) m.p. 123–124°.

Analysis Found: C,51.0; H,5.8; N,10.1.
$C_{13}H_{19}N_3O_2S.C_4H_4O_4.0.1C_2H_6O$ requires C,51.4; H,5.9; N,10.45%.
T.l.c. (K) Rf 0.32

Example 23
N-Methyl-3-[2-(methylamino)ethyl]-1H-indole-5-methanesulphonamide
(a) *3-(2-Chloroethyl)-N-methyl-1H-indole-5-methanesulphonamide.*
A solution of the product of example 6(a) (0.25g) in chloroform (3ml) was added to a solution of polyphosphate ester (2.5g) in chloroform (2ml) and the solution wa heated under reflux with

combined organic extracts gave a pale yellow gum which was chromatographed (J) to give the product as a colourless gum (0.08g). This was dissolved in ethanol (4ml) containing water (0.5ml) and an aqueous solution of creatinine and sulphuric acid (1:1, 2M, 0.14ml) was added. On cooling the *title compound* deposited as a white powder (0.089g), m.p. 197–198°.

Analysis Found: C,42.6;H,5.9;N,16.5.
$C_{14}H_{21}N_3O_2S.C_4H_7N_3O.H_2SO_4$ requires C,42.7;H,6.0;N,16.6%.
T.l.c. (J) Rf 0.37.

Example 27

3-(3-Aminopropyl)-N-methyl-1H-indole-5-methanesulphonamide, compound with hydrogen chloride, water and ether (100:100:85:11).

(a) *2-(5,5-Dimethoxypentyl)-1H-isoindole-1,3(2H)-dione.*

A mixture of potassium phthalimide (0.48g) and 5-bromopentanal dimethyl acetal (0.50g) in dry dimethylformamide (3ml) was stirred at 90° for 5h and then allowed to cool. The resultant yellow suspension was then partitioned between water (30ml) and ethyl acetate (3 × 30ml). The combined organic extracts were then dried (Na_2SO_4) and concentrated *in vauco*.

The residual pale yellow oil was purified by flash chromatography (Kieselgel 9385, ether) to give the title *compound* as a white solid (0.33g), m.p. 34.5°–37°.

(b) *3-[3-(1,3-Dihydro-1,3-dioxo-2H-isoindol-2-yl)propyl]-N-methyl-1H-indole-5-methanesulphonamide.*

A suspension of the product from stage (a) (2.55g) and the product from Example 1(b) (2.50g) in 10% aqueous acetic acid (200ml) was stirred at room temperature for ½h and then at reflux for 1¼h. The yellow gummy suspension was allowed to cool and was then extracted with ethyl acetate (3 × 200ml), dried (Na_2SO_4) and concentrated *in vacuo* to give an orange foam (3.59g). This material was used in stage (C). A portion of this foam (0.50g) was chromatographed (G) to give the impure *title sulphonamide* as an orange foam which failed to crystallised from common organic solvents (0.14g), m.p. 58–66°.

T.l.c. Rf 0.37 (Q)

(c) *3-(3-Aminopropyl)-N-methyl-1H-indole-5-methanesulphonamide, compound with hydrogen chloride, water and ether (100:100:85:11).*

Hydrazine hydrate (3.0ml) was added to a stirred, refluxing suspension of the product from stage (b) (2.90g) in ethanol (90ml) and stirring was continued for 3h. The cooled yellow suspension was evaporated *in vacuo* and the residual yellow solid was partitioned between 2N sodium bicarbonate (150ml) and ethyl acetate (3 × 150ml). The combined organic solutions were then dried (Na_2SO_4) and evaporated *in vacuo*.

The residual yellow foam (1.06) was chromatographed (J) to give an orange gum (0.45g). A portion of this gum (0.39g) was dissolved in absolute ethanol (5ml) and ethanolic hydrogen chloride (1ml) was added. The stirred solution was diluted with dry ether (*ca* 80ml) and the precipitated solid was filtered off, washed with dry ether (4 × 15ml) and dried.

The solid was reprecipitated three times from absolute ethanol (ca 15ml) to give the *title salt* as a hygroscopic brown solid (0.085g) m.p. 121–125° which slowly turned to a gum.

T.l.c.. (J) Rf 0.2.

Analysis Found: C,47.8;H,6.7;N,12.3.
$C_{13}H_{19}N_3O_2S.HCl.0.85H_20.0.11C_4H_{10}O$ requires C,47.3;H,6.7;N,12.3%.

Example 28

Phenylmethyl [2-[5-[[(methylamino)sulphonyl]methyl]-1H-indol-3-yl]ethyl] carbamate.

Sodium hydride (80% in oil, 13mg) was added to a stirred, ice cooled solution of the product from Example 18 stage (a) (150mg) in dry dimethylformamide (3ml) under nitrogen. The suspension was stirred at room temperature for ½h and then cooled in ice. Methyl iodide (0.03ml) was added and the solution stirred at room temperature for 7h with further methyl iodide (.03ml) added after 3h. The solution was partitioned between water (30ml) and ethyl acetate (4 × 20ml). The combined organic extracts were then washed with water (4 × 20ml), dried (Na_2SO_4) and concentrated *in vacuo*. The residual brown oil (140mg) was chromatographed (E) to give the title *carbamate* as a brown oil (16mg). This product was shown by n.m.r. and t.l.c. (E, Rf 0.35) to be identical with the product of Example 2(b).

Example 29

3-(2-Aminoethyl)-N-methyl-1H indole--5-methanesulphonamide

To a solution of the product of example 5(b) (0.1g) and cobaltous chloride hexahydrate (0.19g)

methylcellulose, using standard techniques. Alternatively the tablets may be sugar coated.

Capsules

	mg/capsule
Active ingredient	10.0
* Starch 1500	89.0
Magnesium Stearate BP	1.0
Fill Weight	100.0

* A form of directly compressible starch.

The active ingredient is sieved and blended with the excipients.The mix is filled into size No.2 hard gelatin capsules using suitable machinery. Other doses may be prepared by altering the fill weight and if necessary changing the capsule size to suit.

Syrup

	mg/5ml dose
Active ingredient	10.0
Sucrose BP	2750.0
Glycerine BP	500.0
Buffer, Flavour, Colour, Preservative	as required
Distilled water to	5.0ml

The active ingredient, buffer, flavour, colour and preservative are dissolved in some of the water and the glycerine is added. The remainder of the water is heated to dissolve the sucrose and is then cooled. The two solutions are combined, adjusted to volume and mixed. The syrup produced is clarified by filtration.

Suppositories

Active ingredient	10.0mg
* Witepsol H15 to	1.0g

* A proprietary grade of Adeps Solidus Ph. Eur.

A suspension of the active ingredient in molten Witepsol is prepared and filled, using suitable machinery, into 1g size suppository moulds.

Injection for Intravenous Administration

	% w/v
Active ingredient	0.2
Sodium Chloride BP	as required
Water for Injection BP to	100.00

Sodium chloride may be added to adjust the tonicity of the solution and the Ph may be adjusted, using acid or alkali, to that of optimum stability and/or to facilitate solution of the active ingredient. Alternatively suitable buffer salts may be used.

The solution is prepared, clarified and filled into apporpriate size ampoules sealed by fusion of the glass. The injection is sterilised by heating in an autoclave using one of the acceptable cycles. Alternatively the solution may be sterilised by filtration and filled into sterile ampoules under aseptic conditions. The solution may be packed under an inert atmosphere of nitrogen or other suitable gas.

Inhalation Cartridges

	mg/cartridge
Active ingredient micronised	1.0
Lactose BP	39.0

The active ingredient is micronised (Microniser is a Registered Trade Mark) in a fluid energy mill to a fine particle size range prior to blending with normal tabletting grade lactose in a high energy mixer. The powder blend is filled into No.3 hard gelatin capsules on a suitable encapsulating machine. The contents of the cartridges are administered using a powder inhaler such as the Glaxo Rotahaler (Registered Trade Mark).

Metered Dose Pressurised Aerosol

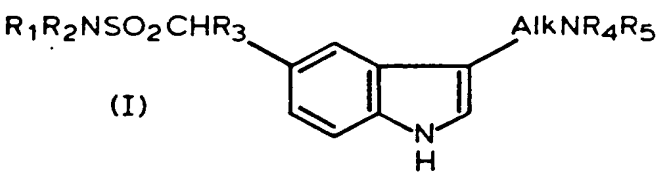
	mg/metered dose	*per can*
Active ingredient micronised	0.500	120.0mg
Oleic Acid BP	0.050	12.0mg
Trichlorofluoro-methane BP	22.250	5.34mg
Dichlorofluoro-methane BP	62.2	14.92g

The active ingredient is micronised in a fluid energy mill to a fine particle size range. The oleic acid is mixed with the trichlorofluoromethane at a temperature of 10–15°C and the pulverized drug is mixed into the solution with a high shear mixer. The suspension is metered into aluminium aerosol cans and suitable metering valves, delivering a metered amount of 85 mg of suspension, are crimped onto the cans and the dichlorodifluoromethane is pressure filled into the cans through the valves.

In the above examples, the active ingredient is preferably 3-(2-aminoethyl)-N-methyl-1*H*-indole-5-methanesulphonamide which may be in the form of a physiologically acceptable salt, for example, the hydrochloride or succinate salt.

CLAIMS

1. A compound of the general formula (I):



(I)

wherein

R_1 represents a hydrogen atom or a C_{1-6}alkyl or C_{3-6} alkenyl group;

R_2 represents a hydrogen atom or a C_{1-3} alkyl, C_{3-6} alkenyl, aryl, ar(C_{1-4})alkyl or C_{5-7} cycloalkyl group;

R_3 represents a hydrogen atom or a C_{1-3} alkyl group;

R_4 and R_5, which may be the same or different each represents a hydrogen atom or a C_{1-3} alkyl or propenyl group or R_4 and R_5 together form an aralkylidene group; and

Alk represents an alkylene chain containing two or three carbon atoms which may be unsubstituted or substituted by not more than two C_{1-3} alkyl groups,

and physiologically acceptable salts and solvates thereof.

2. A compound according to claim 1, wherein, in the general formula (I) R_1 represents a hydrogen atom or a C_{1-6} alkyl group and R_2 represents a hydrogen atom or a C_{1-3} alkyl, C_{3-6} alkenyl or ar(C_{1-4})alkyl group.

3. A compound according to claim 1 or 2, wherein, in the general formula (I), R_3 represents a hydrogen atom.

4. A compound according to any of claims 1 to 3, wherein in the general formula (I), R_4 and R_5, which may be the same or different, each represents a hydrogen atom or a C_{1-3} alkyl group.

5. A compound according to claim 1, wherein in the general formula (I) R_1 represents a hydrogen atom or a C_{1-3} alkyl group, R_2 represents a hydrogen atom or a C_{1-3} alkyl group, a C_{3-4} alkenyl group or an ar(C_{1-2})alkyl group; R_3 represents a hydrogen atom; and R_4 and R_5, which may be the same or different, each represents a hydrogen atom or a C_{1-3} alkyl group.

6. A compound according to claim 5, wherein, in the general formula (I), R_1 represents a hydrogen atom or a C_{1-3} alkyl group; R_2 represent a C_{1-3} alkyl group or a C_{3-4} alkenyl group; R_3 and R_4 each represents a hydrogen atom; and R_5 represents a hydrogen atom or C_{1-3} alkyl group.

7. A compound according to claim 1 selected from 3-(2-methylamino)ethyl)-N-methyl-1*H*-indole-5-methanesulphonamide;

3-(2-aminoethyl)-N,N-dimethyl-1*H*-indole-5-methanesulphonamide;

and physiologically acceptable salts and solvates thereof.

8. 3-(2-Aminoethyl)-N-methyl-1*H*-indole-5-methanesulphonamide and its physiologically acceptable salts and solvates.

9. A compound according to any of claims 1 to 8 wherein the physiologically acceptable salt

wherein Alk is as defined for general formula (I) and Q is a defined in claim 11 or a salt or a protected derivative thereof.

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